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Research Article

Cancer Epidemiology, Biomarkers & Prevention

Association between Statins and Prostate Tumor Inflammatory Infiltrate in Men Undergoing Radical Prostatectomy

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Abstract

Background: Cholesterol-lowering drugs known as statins have been reported to have significant anti-inflammatory properties. Given that inflammation may contribute to prostate cancer progression and that statins may reduce the risk for advanced prostate cancer, we investigated whether statin use was associated with reduced intratumoral inflammation in radical prostatectomy (RP) specimens.

Methods: Inflammation within index tumors of 236 men undergoing RP from 1996 to 2004 was graded by a single pathologist as grade 0 (absent), 1 (mild: ≤10%), and 2 (marked: >10%). Preoperative statin use was analyzed by grouping subjects as statin users or nonusers. Type and dosage of statin was accounted for using dose equivalents with 20 mg simvastatin as reference. Logistic regression was used to determine the association between statin use and intratumoral inflammation controlling for age, race, body mass index, prostate-specific antigen, year of surgery, clinical stage, pathologic Gleason sum, surgical margin status, extracapsular extension, seminal vesicle invasion, prostate weight, time from prostate biopsy to RP, and nonsteroidal anti-inflammatory drug use.

Results: Preoperative statin use was significantly associated with lower risk for any (grade ≥1) intratumoral inflammation (odds ratio, 0.31; 95% confidence interval, 0.10-0.98; $P = 0.047$) on multivariable analysis, with doses ≥20 mg simvastatin equivalents being more strongly associated (relative to nonuse; odds ratio, 0.22; 95% confidence interval, 0.06-0.79; $P = 0.02$).

Conclusion: In a cohort of men undergoing RP, statin use was associated with significantly lower risk of any inflammation within prostate tumors.

Impact: Given previous reports that inflammation is associated with advanced prostate cancer, and statin use is associated with decreased prostate cancer progression risk, our findings suggest that inhibition of inflammation within tumors may be a potential mechanism for purported anti–prostate cancer properties of statins. *Cancer Epidemiol Biomarkers Prev; 19(3); 722–8. ©2010 AACR.*

Introduction

Statins, used for hypercholesterolemia and cardiovascular risk reduction, are the most widely used drug class in Western society due to their efficacy and safety profile (1). The primary mechanism by which statins are thought to decrease cardiovascular disease risk is by lowering cholesterol by inhibiting 3-hydroxy-3-methylglutaryl CoA (HMGCoA) reductase, the rate-limiting step of cholesterol synthesis. However, statins also have other properties, including reducing inflammation. Specifically, statins significantly reduce levels of C-reactive protein

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Author Contributions: L.L. Bañez and S.J. Freedland conceptualized and designed the study; L.L. Bañez, J.C. Klink, J. Jayachandran, A.L. Lark, and L. Gerber acquired the data; L.L. Bañez, J.C. Klink, and S.J. Freedland performed statistical analyses; L.L. Bañez, J.C. Klink, J. Jayachandran, R.J. Hamilton, E.M. Masko, and S.J. Freedland interpreted the data; L.L. Bañez and S.J. Freedland drafted the manuscript; all of the authors performed critical revision of the manuscript; A.L. Lark acquired the histopathologic images for the study; L.L. Bañez, R.T. Vollmer, and S.J. Freedland provided supervision for the study.

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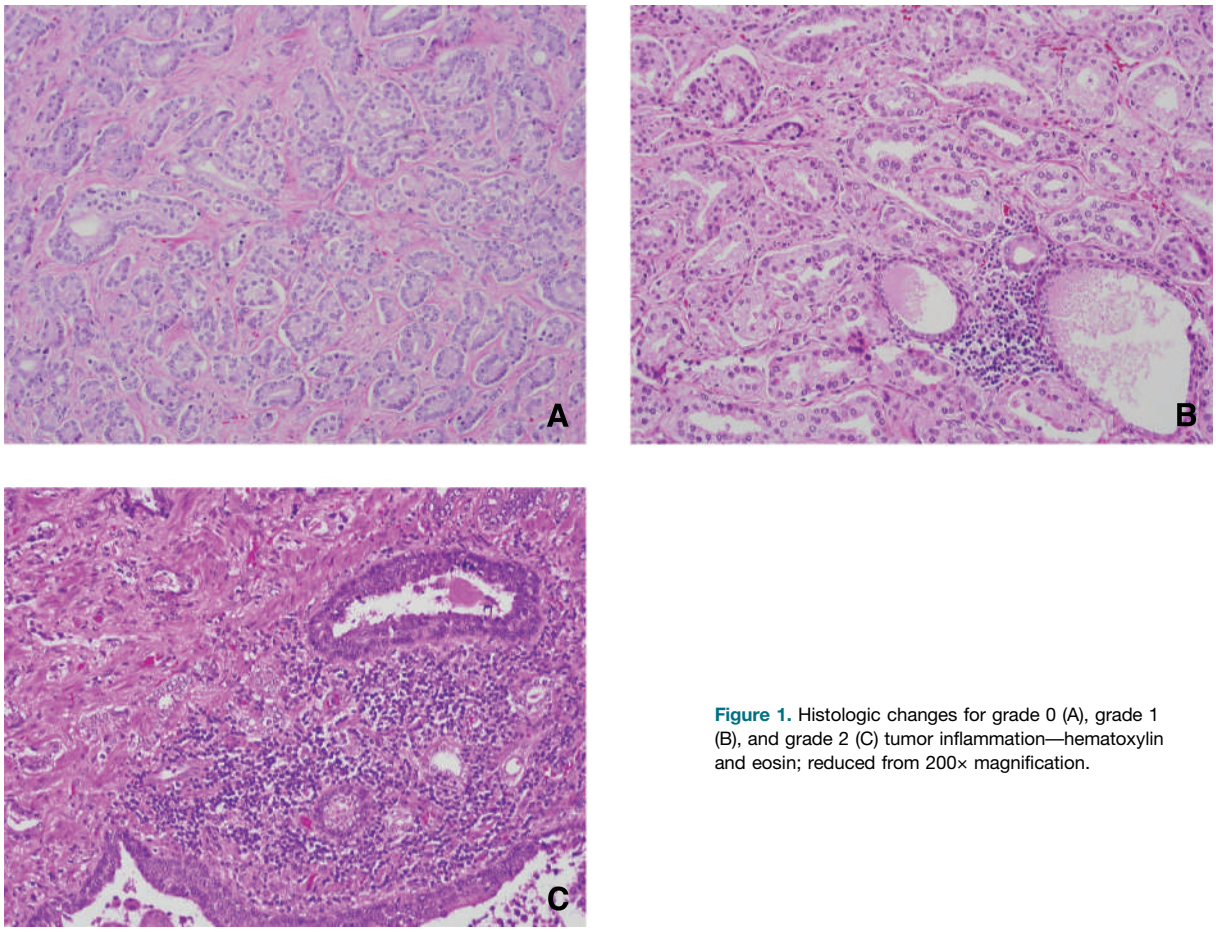

Figure 1. Histologic changes for grade 0 (A), grade 1 (B), and grade 2 (C) tumor inflammation—hematoxylin and eosin; reduced from 200× magnification.

(CRP), an inflammatory marker predictive of future cardiovascular events independent of low-density lipoprotein (LDL) levels (2). Moreover, statins significantly reduce cardiovascular end points and improve overall survival in people with normal cholesterol but elevated CRP levels, suggesting that the anti-inflammatory properties of statins may be crucial for their clinical effect (3). These findings may have profound implications for prostate cancer management as increasing data suggest that inflammation plays a key role in prostate cancer development and progression (4-8).

Epidemiologic evidence suggests that statins may prevent prostate cancer, although not all studies agree (9, 10). More promisingly, four large prospective studies all found that statins reduced advanced prostate cancer risk but not overall prostate cancer risk (11-14). Indeed, similar findings from meta-analyses of randomized controlled trials and large observational studies (15) suggest that although statins may not reduce prostate cancer development, they may prevent prostate cancer progression to more advanced stages. To test this, we recently determined whether statins influenced cancer progression in men undergoing surgical treatment for prostate cancer. We found that statins, in a dose-dependent manner, significantly reduced the risk for recurrence after radical prostatectomy (RP).[6] Given that inflammation is an important process affecting prostate cancer growth and statins have anti-inflammatory properties, it is possible that statins may reduce prostate cancer progression, in part by inhibiting inflammation.

Although statins influence systemic inflammation, it is unknown whether they influence intratumoral inflammation, a pathologic feature reported to correlate with prostate cancer recurrence after surgery (16). We hypothesized that presurgical statin use would decrease the risk for inflammation within prostate tumors. If statins were associated with reduced inflammation within prostate cancer tumors of patients undergoing RP, this would support the hypothesis that statins inhibit prostate cancer progression, in part by suppression of inflammation.

[6] R.J. Hamilton, L.L. Bañez, W.J. Aronson, M.K. Terris, E.A. Platz, C.J. Kane, C.L. Amling, and S.J. Freedland. Statin medication use and the risk of biochemical recurrence following radical prostatectomy: results from the Shared Equal-Access Regional Cancer Hospital database. Unpublished data.

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Materials and Methods

Patient Population

Before analysis, institutional review board approval was obtained through waivers of consent for data collection. A total of 295 men undergoing RP at the Durham Veterans Affairs Medical Center (DVAMC), North Carolina, from 1992 to 2004, who had pathology slides available for review were considered for entry into this study. Men who received neoadjuvant radiation/hormonal therapy (n = 11) were excluded from analysis as these treatments interfere with histopathologic analysis. Likewise, men treated with transurethral resection of the prostate with incidental finding of prostate cancer (clinical T_{1a}/T_{1b}; n = 4) were excluded due to lack of an intact prostate specimen. We further excluded 44 men treated before 1996 because few men (3 of 44) were taking statins before 1996, resulting in a final study population of 236 men.

RP specimens were processed using standardized DVAMC Department of Pathology protocols. Demographic and clinicopathologic information were abstracted from the computerized medical records of DVAMC. To identify statin users, we determined whether a prescription for statins was filled within the year before surgery and abstracted the dose and type of statin using DVAMC pharmacy records. We also determined whether patients filled a prescription for a nonsteroidal anti-inflammatory drug (NSAID), including salicylates, ibuprofen, naproxen, etc., within the year before RP.

Inflammation Grading

Hematoxylin and eosin–stained archival tissue slides were reviewed by a single pathologist (R.T.V.) to select the index tumor. A second pathologist (A.L.L.), who was blinded to clinical information, graded for inflammation within the index tumor according to the following scoring system: grade 0 (absent: no inflammation; Fig. 1A), grade 1 (mild: ≤10% tumor inflammation; Fig. 1B), and grade 2 (marked: >10% tumor inflammation; Fig. 1C). Only lymphoid nodules and inflammatory cells surrounding malignant glands and ducts were considered as tumor inflammation. Inflammation associated with benign glands and surrounding stroma was excluded. There was no attempt to grade the degree of epithelial cell destruction by inflammation or to distinguish preponderance of acute versus chronic inflammatory cells within the infiltrates. In exploratory univariate and multivariate analyses, the risk of biochemical recurrence was increased and similar among men with either grade 1 or grade 2 inflammation relative to men with no inflammation. Thus, inflammation was dichotomized as an absent/present outcome variable.

Statistical Analysis

Distribution of clinicopathologic characteristics was compared between statin users and nonusers using χ^2 test for categorical variables and Wilcoxon-Mann-Whitney test for continuous variables. We used multivariate logistic regression to determine the independent association of statin use with tumor inflammation. Statin use was initially analyzed as a yes/no variable. Accounting for type and dosage, statin use was also analyzed as dose equivalents (DE) based on reported guidelines, with 20 mg simvastatin being assigned a value of 1 (17). Because few patients were on very high (≥4) or very low (<0.5) DEs, statins were analyzed categorically as nonuser, <1, 1, and >1 DE. Variables included in the multivariable model predicting tumor inflammation included age (continuous), race (Caucasian, African American, other), body mass index (BMI <25.0, 25.0-29.9, 30.0-34.9, ≥35 kg/m^2), preoperative prostate-specific antigen (PSA; continuous after logarithmic transformation), year of surgery (continuous), clinical stage (T_{1c}, T_2/T_3), pathologic Gleason sum (2–6, 7, 8–10), positive surgical margins (yes/no), extracapsular extension (yes/no), seminal vesicle invasion (yes/no), prostate specimen weight (continuous after logarithmic transformation), and NSAID use (yes/no). Lymph node status was not included in the regression model due to very few men with lymph node involvement (n = 2). We also controlled for the number of days between prostate biopsy and surgery (continuous after logarithmic transformation) to account for a potential effect the biopsy procedure may have on tumor inflammation.

All analyses were done using STATA 10 (StataCorp). All tests for statistical significance were two-sided with an α of 0.05.

Results

Baseline Patient Characteristics

Thirty-seven patients (16%) took statins the year before surgery, with simvastatin being the most common (92%; Table 1). More than half of the patients (52%) were Caucasian and 66% were overweight or obese. Most tumors (57%) were detected through an elevated PSA (clinical stage T_{1c}) with a median time from diagnosis to surgery of 56 days (interquartile range 36-101 days). Although statin users underwent surgery in more recent years (P = 0.01) and had higher biopsy Gleason sums (P = 0.007), there were no significant differences with regard to age, race, PSA, BMI, NSAID use, clinical stage, or time between biopsy to surgery. Furthermore, there were no significant differences in histopathologic tumor features (pathologic Gleason sum, margin status, extracapsular extension, seminal vesicle invasion, lymph node metastasis, and prostate weight) between statin users and nonusers. Overall, biochemical recurrence occurred in 42% of patients after a median postoperative follow-up of 63 months.

Statins and Tumor Inflammation

Most patients (82%) had inflammatory infiltrates in their prostate tumors. Among patients with inflammation,

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Table 1. Distribution of study population according to demographic/clinicopathologic characteristics and statin use (N = 236)

	Statin users	Nonusers	P*
n (%)	37 (16)	199 (84)	
Age (y)			0.63†
Median (IQR)	64 (59-67)	63 (58-67)	
Type of statin (%)			
Simvastatin	34 (92)		
Atorvastatin	3 (8)		
Statin dose equivalent (%)			
<20 mg simvastatin	10 (27)		
20 mg simvastatin	14 (38)		
>20 mg simvastatin	13 (35)		
Inflammation grade (%)			0.63
Grade 0	8 (22)	34 (17)	
Grade 1	17 (46)	108 (54)	
Grade 2	12 (32)	57 (29)	
Race			
Caucasian	24 (65)	99 (50)	
African American	13 (35)	96 (48)	
Other	0 (0)	4 (2)	
Year of surgery			0.01†
Median (IQR)	2001 (2001-2003)	2000 (1998-2002)	
PSA			0.53†
Median (IQR), ng/mL	8.1 (5.2-13.0)	7.6 (5.2-11.1)	
BMI (%), kg/m^2			0.35
<25	8 (25)	60 (35)	
25-29.9	12 (37)	67 (40)	
30-34.9	11 (34)	35 (21)	
≥35	1 (3)	8 (5)	
NSAID use before RP	27 (73)	114 (57)	0.07
Biopsy Gleason sum (%)			0.007
2-6	17 (46)	130 (66)	
7	11 (30)	52 (26)	
8-10	9 (24)	16 (8)	
Clinical stage (%)			0.75
cT_1	23 (62)	111 (62)	
cT_2/cT_3	14 (38)	76 (41)	
Time interval from biopsy to RP			0.38†
Median (IQR), d	76 (36-103)	55 (36-96)	
Pathologic Gleason sum (%)			0.10
2-6	2 (5)	40 (20)	
7	31 (84)	138 (69)	
8-10	4 (11)	21 (11)	
Extracapsular extension (%)	13 (35)	49 (25)	0.19
Positive surgical margins (%)	27 (73)	126 (63)	0.26
Seminal vesicle invasion (%)	8 (22)	28 (14)	0.25
Lymph node involvement (%)			0.38
Negative	16 (43)	81 (41)	
Positive	1 (3)	1 (0.5)	
Not assessed	20 (54)	117 (59)	
Prostate weight			0.12†
Median (IQR), g	40 (32-52)	36 (29-46)	

Abbreviation: IQR, interquartile range.
*Using χ^2 test unless otherwise specified.
†Using Wilcoxon-Mann-Whitney test.

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Table 2. Frequency by inflammation grade and association of clinical characteristics with tumor inflammation grade ≥1 in men undergoing RP

	Inflammation grade		OR (95% CI)	*P*
	0 (%)	≥1 (%)		
Statin medication usage*				
Nonusers	34 (81)	165 (85)	Reference	
<1 DE	1 (2)	9 (5)	1.30 (0.08-22.02)	0.86
≥1 DE	7 (17)	20 (10)	0.22 (0.06-0.79)	0.02
Race				
Caucasian	18 (43)	105 (54)	Reference	
African American	22 (52)	87 (45)	0.64 (0.25-1.61)	0.34
Other	2 (5)	2 (1)	0.22 (0.01-4.14)	0.31
BMI (kg/m^2)				
<25	12 (31)	56 (34)	Reference	
25-29.9	16 (42)	63 (38)	0.93 (0.32-2.71)	0.89
30-34.9	9 (24)	37 (23)	0.58 (0.16-2.02)	0.39
≥35	1 (3)	8 (5)	0.99 (0.07-14.09)	0.99
Clinical stage				
T_{1c}	30 (77)	104 (56)	Reference	
$T_{2/T3}$	9 (23)	81 (44)	3.42 (1.17-10.03)	0.025
NSAID use before RP	26 (62)	115 (59)	1.09 (0.41-2.87)	0.87
Pathology Gleason sum				
2-6	12 (29)	30 (15)	Reference	
7	26 (62)	143 (74)	1.43 (0.45-4.54)	0.55
8-10	4 (9)	21 (11)	0.45 (0.07-2.87)	0.40
Extracapsular extension	5 (12)	57 (30)	3.42 (0.82-14.27)	0.09
Positive surgical margins	20 (48)	133 (69)	2.00 (0.80-5.03)	0.14
Seminal vesicle invasion	2 (5)	34 (18)	4.79 (0.44-52.12)	0.20

NOTE: Data were obtained by using logistic regression controlling for age, year of surgery, time interval from biopsy to surgery, and prostate weight in addition to parameters listed in the table.
*Usage of statin medication was expressed in DE terms, with simvastatin 20 mg as 1 DE.

36% had marked tumor inflammation. Overall statin use was significantly associated with lower risk for any tumor inflammation [odds ratio (OR), 0.31; 95% confidence interval (95% CI), 0.10-0.98; $P = 0.047$]. When statin use was treated as a four-tiered categorical variable (nonuser, <1, 1, and >1 DE) in multivariate analysis, compared with nonusers, statin use <1 DE was not significantly associated with inflammation (OR, 1.56; 95% CI, 0.08-28.84). However, higher statin doses such as 1 DE (OR, 0.12; 95% CI, 0.02-0.62) and >1 DE (OR, 0.48; 95% CI, 0.07-3.44) were associated with reduced risk of inflammation, although only the association for 1 DE reached statistical significance. Based on similar trends for reduced inflammation for statin users of both 1 and >1 DE, we grouped men taking statins with doses equivalent to or greater than 20 mg simvastatin together and treated statin use as a three-tiered categorical variable (nonuser, <1, and ≥1 DE). After controlling for multiple preoperative and postoperative covariates, statin use ≥1 DE was significantly associated with lower risk for any tumor inflammation ($P = 0.02$; Table 2). Factors that were associated with the presence of tumor inflammation were older age ($P = 0.005$), higher clinical stage ($P = 0.025$), and longer time from biopsy to surgery ($P = 0.003$).

Discussion

Statins significantly reduce the incidence of cardiovascular events even in individuals with normal cholesterol levels (3). With regard to prostate cancer, increasing evidence suggests that statins may reduce the risk of advanced prostate cancer (11-14). Moreover, we previously found preoperative statin use to be associated with reduced prostate cancer progression risk.[7] It has even been hypothesized that statin use contributed to the decline in prostate cancer mortality in the United States over the last 15 years, a time period when statin use increased dramatically (18). However, the underlying biological

[7] R.J. Hamilton, L.L. Bañez, W.J. Aronson, M.K. Terris, E.A. Platz, C.J. Kane, C.L. Amling, and S.J. Freedland. Statin medication use and the risk of biochemical recurrence following radical prostatectomy: results from the Shared Equal-Access Regional Cancer Hospital database. Unpublished data.

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mechanisms through which statins are associated with decreased prostate cancer progression risk are not well defined. In the current study, we found that statin intake before surgery was significantly associated with reduced risk of inflammation surrounding malignant glands within RP specimens, suggesting that statins may have anti-inflammatory effects within prostate cancer. If validated in confirmatory studies, these findings support the hypothesis that statins delay prostate cancer progression, in part by reducing inflammation within the tumor.

Although evidence for statins preventing overall prostate cancer remains uncertain, there is growing data supporting that statins may lower the risk of advanced prostate cancer. Four recent large prospective studies all found that statin users had reduced risk for advanced prostate cancer, although the number of men with advanced disease in these studies was small (11-14). The Health Professionals Follow-up Study, the first to be reported, examined 34,989 U.S. male health professionals who were cancer-free in 1990 and followed until 2002 (11). Statin use was associated with a 49% risk reduction for advanced prostate cancer and a 61% risk reduction for metastatic or fatal prostate cancer. Among men reporting ≥5 years of statin usage, advanced prostate cancer risk was reduced by 74%. Similar findings were published among subscribers of an integrated health care program in northern California, which showed a 32% risk reduction for nonlocalized prostate cancer among statin users reporting >5 years of usage (15).

The anti-inflammatory effects of statins are well documented from a cardiovascular risk reduction viewpoint (2, 3). Most compelling is that statins lower serum levels of CRP in a manner independent of LDL reduction (2). The fact that this effect is independent of LDL reduction is supported by data showing that ezetimibe, a nonstatin cholesterol-lowering agent, significantly lowers LDL levels but has no effect on CRP (19). Also, statins reduce the incidence of graft rejection and arteriopathy in cardiac transplant patients by reducing cytotoxicity of natural killer cells (20). Although it is plausible that systemic anti-inflammatory properties of statins would affect prostate tumors, no studies to date have tested this postulate. In our study, we found a significant risk reduction for tumor inflammation among statin users independent of demographic and clinicopathologic characteristics, suggestive of statin-related anti-inflammatory activity within prostate tumors. Moreover, this association was even stronger after accounting for statin dosage as ≥20 mg simvastatin DE was associated with decreased risk for any intratumoral inflammation. Notably, clinical factors that may influence tumor inflammation were adjusted for, such as BMI and NSAID use. As this is the first study to show such an effect, these novel findings require external validation.

Our study had several limitations. First, our sample size was small and thus subject to type I error. Second, assaying for other molecular markers of inflammation and characterizing the inflammatory cells within the infiltrate would be informative. However, examining the presence or amount of inflammatory infiltrate is a vital preliminary investigation as this pathologic hallmark has previously been correlated with prostate cancer outcomes (16). Third, we noted similar recurrence risk for mild and moderate/severe inflammation. Whether this reflects that the presence of inflammation is sufficient to increase risk or that a 10% cutoff is not optimal to risk stratify patients requires further study. Fourth, we were unable to account for over-the-counter drugs that have anti-inflammatory properties. However, we adjusted for prescription NSAID use. Last, as simvastatin constituted >90% of statins used, future studies are necessary to confirm whether similar associations are seen with other statins.

Conclusions

Preoperative statin use was significantly associated with risk reduction for intratumoral inflammation among prostate cancer patients undergoing RP. As this is the first study to show such an association, these findings require confirmation. However, given that tumor inflammation has been reported to be associated with increased risk for prostate cancer progression, inhibition of inflammation may be a potential mechanism that could explain why men on statins have lower risk for advanced prostate cancer.

Disclosure of Potential Conflicts of Interest

L.L. Bañez reported to be an investigator for an investigator-initiated research grant from AstraZeneca Pharmaceuticals LP; S.J. Freedland reported to be on the speakers' bureau and advisory board for AstraZeneca Pharmaceuticals LP.

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